Aerobic exercise impacts the tumor microenvironment by altering CAF abundance and composition in pancreatic cancer

Riccardo Ballarò, PhD

Background/hypothesis

- Tumor mass
- Peritoneal carcinomatosis
- Desmoplasia
- CAF abundance
- CAF subtype distribution
- Cytokine expression

Methods

- Treadmill adaptation
- Exercise
- 45 min/day at 8 m/min or 16 m/min
- 5 days a week
- Injection
- Ultrasound and randomization
- Ultrasound (tumor volume around 30 mm³)
- Ultrasound
- Ultrasound
- Ultrasound
- Euthanization
- 1.25 x 10^5 KPC 4662 cells in pancreata of 8-week-old female mice
Exercise at 8 and 16 m/min does not impact on PDAC growth, spreading and desmoplasia

Exercise at 8 and 16 m/min reduces CAF abundance in PDAC

Exercise at 8 and 16 m/min impacts on CAF subtype distribution in PDAC

Exercise at 8 and 16 m/min reduces the expression of CAF-related cytokines in PDAC

**Results**

**Day 32**

<table>
<thead>
<tr>
<th>Tumor mass</th>
<th>Control</th>
<th>8 m/min</th>
<th>16 m/min</th>
<th>NG2+ CAFs</th>
<th>αSMA+ CAFs</th>
<th>myCAF/iCAF ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0</td>
<td>0.5</td>
<td>1.0</td>
<td>0.0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>0.0</td>
<td>0.5</td>
<td>1.0</td>
<td>0.0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**Desmoplasia**

- **Masson's trichrome**
- **Hyaluronic acid**

**Exercise at 8 and 16 m/min reduces the CAF abundance in PDAC**

**Exercise at 8 and 16 m/min impacts on CAF subtype distribution in PDAC**

**Exercise at 8 and 16 m/min reduces the expression of CAF-related cytokines in PDAC**

**Whole tumor**

- **Tnf**
- **Il1b**
- **Tgfb1**

**FACS-isolated CAFs**

- **Single cell dissociation**
- **Live cells**

**Exercise at 8 and 16 m/min reduces the expression of CAF-related cytokines in PDAC**

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**Exercise at 8 and 16 m/min reduces the expression of CAF-related cytokines in PDAC**

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**FACS-isolated CAFs**

- **Single cell dissociation**
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**Exercise at 8 and 16 m/min reduces the expression of CAF-related cytokines in PDAC**
Conclusions

<table>
<thead>
<tr>
<th>PDAC</th>
<th>8 m/min</th>
<th>16 m/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth and invasion</td>
<td>No change —</td>
<td>No change —</td>
</tr>
<tr>
<td>Desmoplasia</td>
<td>No change —</td>
<td>No change —</td>
</tr>
<tr>
<td>CAF abundance</td>
<td>Reduces</td>
<td>Reduces</td>
</tr>
<tr>
<td>myCAF/iCAF ratio</td>
<td>Increases</td>
<td>Increases</td>
</tr>
<tr>
<td>CAF-related cytokine expression</td>
<td>Reduces</td>
<td>Reduces</td>
</tr>
</tbody>
</table>

- Exercise decreases the total amount of CAFs and alters the CAF composition by increasing myCAF and reducing iCAF.
- Due to the relevance of the CAF heterogeneity in PDAC chemoresistance and immunosuppression, further studies are needed to test the synergistic effect of exercise with chemotherapy or ICB on tumor growth.

Thanks for your attention

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